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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,004	01/03/2001	Marc Feldmann	65019-DA-PCT-US/JPW/AJM	2757

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,004	FELDMANN ET AL:	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/4/04; 12/3/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,6 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6, 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.
Applicant's submission, filed on 12/3/04, has been entered.

Applicant's amendment, filed 8/4/04, has been entered.
Claims 3-5, 7-10 and 18-38 have been canceled
Claims 1, 2 and 11 have been amended.

Claim 1, 2, 6, and 11-17 are under consideration as the claims read on the use of anti-TNFα antibodies as the TNFα antagonist in the instant application

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 8/4/04.
The rejections of record can be found in the previous Office Actions.

While it is noted that applicant has amended the claims and has provided additional evidence to support the asserted unexpected results,
applicant's arguments and the examiner's rebuttal appear to be essentially the same of record, particularly given the priority of the instant claims. (See the next Section).

3. Applicant's assertions that the instant claims receive priority back to USSN 07/958,248, filed 10/8/92, as well as USSN 08/403,785, filed 5/3/95 (now U.S. Patent No. 5,741,488), are not found convincing for the following reasons.

USSN 07/958,248 does not appear to provide adequate written support for
"preventing",
"TNFα antagonists",
"in a series of doses separated by intervals of days or weeks" as it reads on TNFα antagonists or TNFα-specific antibodies"AND methotrexate (versus anti-CD4 antibodies and anti-TNF antibodies; see page 5 and 9-10 of USSN 07/958,248 as cited by applicant);
"said TNFα antagtonist prevents TNFα synthesis or "TNFα release",
"cA2" and "competitively inhibits binding of TNFα to monoclonal cA2" or
"binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO 1 and 2".

While priority applications USSNs 07/945,248 and PCT/GB94/00462 may have "incorporated by reference" the teachings of a number of references, including USSN 07/943,852 for a detailed description of anti-TNF antibodies and their use in the treatment of diseases (e.g. see page 8 of USSN 07/945,248),
mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144, (CCPA 1973).

In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication.
Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.
Applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re de Seversky, 177 USPQ 144, 146 (CCPA 1973).

It does not appear that applicant's priority applications, including USSNs 07/945,249 and 08/403,785 as well as /GB94/00462 provide sufficient specificity and particularity as to what specific material is being incorporated. See "limitations" above.

Further, it is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

It does not appear that the written description and incorporation by reference relied upon in applicant's asserted priority is sufficient to provide said priority.

As pointed out previously, the filing date of the instant claims is deemed to be the filing date of parent application USSN 08/690,775, i.e. 8/1/96.

If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C.§ 112, first paragraph.

The examiner appreciates setting forth the information in charts in aiding a determination of priority of the instant claims.

4. Claims 1, 2, 6, 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mak et al. (U.S. Patent No. 6,190,691) (1449; #AK) (see entire document) essentially for the reasons of record.

Applicant's arguments, filed 8/4/04, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Actions.

As pointed out in the Section above, applicant's instant claims do not receive a priority date that precedes the 102(e) date of Mak et al. (U.S. Patent No. 6,190,691).

The following is reiterated for applicant's convenience.

Again, applicant essentially argues that the teachings of Mak result in a combined total of examples numbering in the hundreds. Applicant further asserts that there is no specific disclosure of the claimed combination of methotrexate and a TNFα antagonist. Applicant asserts that the combination of agents used in the claimed invention represents only one of an astronomical number of permutations of the pharmacological agents disclosed by Mak.

In contrast to applicant's assertions, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. See Ex parte A, 17 USPQ2d (Bd. Pat. App. & Inter. 1990) and MPEP 2131.02.

As pointed out previously, Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies and fragments thereof (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules encompassed by the claimed methods (columns 53-56) to treat psoriasis and psoriatic rheumatism (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns 59-61, Treatment of Skin Diseases).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations, including the epitope specificities and dosing schedules would be inherent properties of the referenced methods to treat psoriasis and psoriatic rheumatism with anti-TNF antibodies and methotrexate. Given the inhibitory properties of the referenced anti-TNF antibodies, the claimed functional properties and epitope specificities, including the cA2 competing antibodies would have been inherent properties of the referenced anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) .

Applicant's arguments are not found persuasive.

5. Claims 1, 2, 6, 11-13 and 16-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691) AND/OR Adair et al. (U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437) and Aggarwal et al. (U.S. patent No. 5,672,347) (1449, #AF) essentially for the reasons of record.

Applicant's arguments, filed 8/4/04, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Actions.

Applicant asserts that a prima facie case of obviousness has not been established.

Applicant's arguments and the examiner's rebuttal concerning Mak is addressed above.

Applicant's reliance upon Verhoeven et al., British Journal of Rhematology 37: 612-619, 1998 (of record) and newly submitted Genovese et al., Arthritis and Rheumatism 50: 1412-1419, 2004 is acknowledged.

Here, applicant underscores their position that many combinations of drugs do not improve treatment of human patients with active rheumatoid arthritis and the superior effects of a particular combination therapy in the treatment of inflammatory disease are not predictable absent experimentation.

It appears that neither Verhoeven et al. nor Genovese et al. describe the unexpected results of combining anti-TNF antibody with methotrexate.

For example, Verhoeven et al. describe combinations of non-antibody antagonists of disease modifying anti-rheumatic drug therapy and Genovese et al. describes combinations of anti-cytokine antibody antagonists.

It is noted that the patients described by Genovese et al. are receiving stable doses of methotrexate and other medications (e.g. corticosteroids) throughout the study (see Study Design and Treatment on page 1413, column 1). Therefore, it appears that Genovese et al. supports the baseline treatment of arthritis patients with methotrexate coupled with other known anti-inflammatories such as corticosteroids along with an additional arthritic antagonists such as TNF antagonists, including anti-TNF antibodies. The lack of benefit of combination therapy based upon anti-IL-1 antibody therapy and anti-TNF antibody therapy may have been attributed to the degree of overlap and interplay between IL-1 and TNF (see page 1418, column 1, paragraph 1 of Genovese et al.). There is insufficient objective evidence to suggest that there would have an expectation of negative interactions of administering known methotrexate therapy for arthritis patients along with the prior art teaching of anti-TNF antibody to treat the same patients.

Applicant is invited to consider addressing the issues of dosing such that therapeutically effective amounts which are not necessarily an amount such that administration of the TNF antagonist alone or the administration of methotrexate alone would result in inhibition of the biological activity of TNF (e.g. see page 26, lines 32-35 of the instant specification).

The record, including Genovese et al., appears to be consistent with the prior art rejection of record that the ordinary artisan would have had an expectation of success in combining the standard or common practice of treating psoriatic arthritis patients with methotrexate (and corticosteroids) coupled with an antagonist such as anti-TNF antibody, which acts via a different mode of action from such DMARDs and specifically targets an important inflammatory cytokine associated with the arthritis.

With respect to dosing, it is noted that Mak et al. teach the well known position that the optimal combination of therapies and their sequence will depend upon the type of disorders to be treated, the severity and course of that disorder, previous therapy, the patient's health status and response to drugs and the judgment of the treating physician (e.g. column 53, paragraph 3).

Similarly, Adair et al. teach that the dose at which the antibody is administered depends on the nature of the condition to be treated, the degree to which the TNF to be neutralized is or is expected to be (e.g. see column 12, paragraph 6)

Further, it is noted that the Merck Manual does teach that methotrexate has been widely used to treat rheumatoid arthritis and can be given 2.5. to 15 mg in a single dose weekly, which is usually started at 7.5 mg/wk (see page 1311, Cytotoxic or Immunosuppressive Drugs). Here, too, is mentioned the side effects of such treatment. Therefore, the ordinary artisan recognized that the additional benefit of combining an immunosuppressive such as anti-TNF antibody would be the possible reduction in the amount of methotrexate administered, which in turn, would result in decreased side effects for these patients undergoing long term treatment.

Again, applicant asserted that the methods of the instant invention has provided for the surprising discovery of an unexpected advantage or synergistic effects over the treatment of each agent alone.

It is noted that "synergistic amounts" is not recited in the instant claims

Applicant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997)

In contrast to applicant's assertions, the prior art provides sufficient motivation and expectation success of combining anti-TNF antibodies and methotrexate in the treatment of inflammatory conditions, including psoriasis and psoriatic rheumatism.

As pointed out previously, the following of record is reiterated for applicant's convenience.

Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules (columns 53-56) to treat psoriasis and psoriatic rheumatism (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns 59-61, Treatment of Skin Diseases). Mak et al. differs from the claimed invention by not disclosing the well known use of recombinant antibodies.

Adair et al. teach the use of recombinant anti-TNF antibodies and fragments thereof to treat autoimmune diseases, including psoriasis and arthritis (see column 11, paragraph 8), alone or in combination with other active ingredients (column 11, paragraph 5), including well known methods of modes of administration (column 12)(see entire document). Adair et al. differs from the claimed methods by not disclosing the well known use of methotrexate in the treatment of psoriasis and psoriatic arthritis

Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992) disclose the well known use of methotrexate in the treatment of psoriasis and psoriatic arthritis; pages 1338 and 2435-2437).

Given the teachings of Mak et al., Adair et al. and the Merck Manual of Diagnosis and Therapy, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of anti-TNF antibodies in combination with the immunosuppressant methotrexate to treat psoriasis and psoriatic rheumatism (e.g. psoriatic arthritis). Given the inhibitory properties of the referenced anti-TNF antibodies by Mak et al. and Adair et al., the claimed functional and epitope specificities, including the cA2 competing antibodies would have been expected or intrinsic properties of the referenced anti-TNF antibodies. Providing the claimed recombinant anti-TNF antibodies and fragments thereof encompassed by the instant claims (e.g. chimeric, humanized, resurfaced antibody) would have been obvious to the ordinary artisan to provide therapeutic antibodies in order to decrease the immunogenicity of therapeutic antibodies and to increase half-life of antibodies to achieve effective amounts of anti-TNF antibodies. Rheumatism refers to a variety of disorders marked by inflammation, degeneration or metabolic derangement of the connective tissue structures, including The joints and when it is confined to joints it refers to arthritis. The Merck Manual notes that psoriasis is associated with joint involvement known as psoriatic arthritis. The various therapeutic modalities are either explicitly taught by Mak et al. or would have been obvious to one of ordinary skill in the art to provide effective therapeutic amounts of immunosuppressive regimens in order to meet the needs of the patients, herein, patients with psoriasis and psoriatic arthritis.

In addition to teaching the use of anti-TNF antibodies to treat various autoimmune diseases, Aggarwal et al. teach that the combination of TNF antagonists and anti-inflammatory agents provides for the use of these agents in lesser dosages when used alone. An ordinary artisan would have been motivated to provide anti-TNF antibodies to lessen the amount of methotrexate, given its know toxicities at the time the invention was made. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See MPEP 2144.06. Here, the prior art teaches combining antagonists encompassed by the claimed invention by teaching the use of anti-TNF antibodies and/or methotrexate to treat psoriasis and psoriatic arthritis with other agents to inhibit the same disease. Here, too, the references teach the art known advantages of employing two immunosuppressives at the time same time, as evidenced by Aggarwal. et al.

While applicant assertions of unexpected results in combination with Verhoeven et al. and Genovese et al.. are acknowledged, the prior art clearly provide the rationale for combining anti-TNF antibodies in combination with methotrexate in a recognition in the art that there were advantages or beneficial results produced by their combination. Therefore, in this instance, there was sufficient motivation and expectation of success in combining anti-TNF antibodies and methotrexate in the treatment of psoriasis and psoriatic arthritis at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

Applicant's arguments are not found persuasive.

6. Claims 14-15 are rejected under 35 U.S.C. ə 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691)(1449; AK) AND/OR Adair et al. (U.S. Patent No. 5,994,510) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437)and Aggarwal et al. (U.S. patent No. 5,672,347) (1449, #AF),
as applied to claims 1, 2, 6,11-13 and 16-17 above and further in view of Le et al. (U.S. Patent No. 5,919,452) (1449; # AD) for the reasons of record set forth in the previous Office Actions.

Applicant's arguments, filed 8/4/04, have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Actions and addressed herein.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above. Applicant's arguments are not found persuasive.

7. Claims 1, 2, 6 and 11-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

Applicant intends to filed a terminal disclaimer with respect to the '766 patent once the claims are otherwise in condition for allowance.

8. Given applicant's amended claims, the previous provisional rejection under 35 U.S.C. 101 as claiming the same invention as that of pending claims of copending application USSN 09/921,937 has been withdrawn.

Claims 1, 2, 6 and 11-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 55, 60, 70-87 of copending USSN 09/921,937. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claim sets are drawn to methods of treating arthritic conditions with the same TNFα-specific antibodies. Given the role of TNFα in various inflammatory conditions, including various arthritic conditions such as the psoriatic arthritis of the instant application or arthritis / rheumatoid arthritis of the copending application, one of ordinary skill in the art would have been motivated to treat the various arthritic conditions with the same TNFα-specific antibodies to neutralize the ill-effects of inflammatory TNFα with an expectation of success.

Applicant's request for holding double patenting rejection over copending USSN 09/921,937 until one of the two applications is allowed is acknowledged.

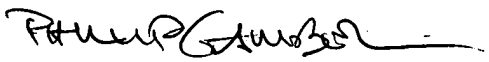
This obvious double patenting rejection is maintained.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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March 4, 2005